

**Amendment and Response**

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Serial No.: 10/817,530

Confirmation No.: 4868

Filed: April 2, 2004

For: PHYSICAL-CHEMICAL PROPERTY BASED SEQUENCE MOTIFS AND METHODS REGARDING  
SAME

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**Remarks**

The Office Action mailed 7 February 2007 has been received and reviewed. Claims 1 and 12 have been amended and claim 4 has been canceled. Therefore, the pending claims are claims 1-3 and 5-22. Reconsideration and withdrawal of the rejections are respectfully requested in view of the amendments and remarks provided herein.

**Prior Restriction Requirement**

Applicant acknowledges the Examiner's withdrawal of the previous Restriction Requirement, as well as the consideration of all pending claims 1-22 in the present Office Action.

**Information Disclosure Statement**

Applicant acknowledges that the Information Disclosure Statement filed on 20 April 2005 has only been partially considered. However, Applicant has no manner of determining a publication date for the documents retrieved from the Internet, and as such, must rely on the retrieval date as the date which Applicant knows the documents were available. Therefore, unless the Examiner requests further information regarding such documents, Applicant believes its duty with respect to such documents is satisfied.

**Sequence Compliance**

The Examiner has indicated that Figure 9A contains sequences with no associated SEQ ID NOs. The SEQ ID NOs. are provided by amendment to the Brief Description of the Drawings section of the application. A Supplemental Sequence Listing is submitted herewith which includes those sequences listed in Figure 9A.

**Specification**

The Examiner objected to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code. Paragraphs including such links have been amended to make any language provided therein non-executable. As such, the objection is overcome.

Further, the Examiner objected to the use of the alleged trademark BLAST, for example, at page 18. However, it is Applicant's belief that the term BLAST is an acronym for basic local alignment search tool used by those skilled in the art, and is not generally used as a trademark. If the Examiner is aware of an owner claiming trademark rights in the term BLAST, Applicant would be willing to amend the specification accordingly. As such, it is believed that the objection to the improper use of this trademark is overcome.

**The 35 U.S.C. §101, Rejection**

The Examiner rejected claims 1-22 under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. Specifically, the Examiner alleges that there is "no actual, concrete result" that is "recited in the claims, nor is any useful result 'produced' in a tangible form useful to one skilled in the art." Applicants respectfully traverse this rejection.

As presented in the amended claims, the present invention is a method for use in sequence data analysis, or a computer program for use with a processing apparatus to analyze sequence data. Even before amendment to the claims, the definition of one or more PCP motifs in the multiple sequence alignment provides an actual, concrete result that was recited in the claims. Such defined PCP motifs are clearly tangible and useful to one skilled in the art, e.g., for use in searching a sequence database to identify related sequence segments. Such a task is unquestionably useful, particularly in the field of biotechnology research and development.

In other words, a first output of the method and/or program are defined PCP motifs (e.g., a defined group of protein sequences). For example, such defined PCP motifs may be matrices of numbers that represent the average value of each of 5 eigenvectors from the multidimensional

scaling analysis of the amino acid properties at each position in the motif as described in the specification. Such PCP motifs are defined, tangible and concrete, and they can be used to scan databases for proteins that contain similar motifs, which can be identified, for example, in a statistically significant fashion.

Moreover, to move the application to issuance, the claims were amended to further indicate that the one or more PCP motifs are used to search a sequence database "resulting" in identification of one or more related sequence segments having PCP characteristics similar to one or more of the PCP motifs. As such, not only are the defined PCP motifs an actual, concrete result recited in the claims and tangible for use to one skilled in the art in searching a sequence database, the resulting identified "one or more related sequence segments having PCP characteristics similar to one or more of the PCP motifs" are also an actual, concrete result recited in the claims and tangible for use to one skilled in the art.

In other words, a second output of the method and/or program are one or more related sequence segments having PCP characteristics similar to one or more of the PCP motifs (e.g., a list of proteins from large databases that contain sequences that are statistically significant to the motif lists).

As such, contrary to the Examiner's allegations, the defined PCP motifs, as well as the identified related sequence segments, are a very useful, concrete, and tangible result. For example, one or more program routines provide such useful, concrete and tangible results, and its usefulness is unquestionable.

If for some reason the Examiner still does not consider the claims to be statutory subject matter, the Examiner is requested to contact Applicants' attorney identified herein to further discuss this matter and discuss any suggested amendments to move this case to issuance.

### **The 35 U.S.C. §112, Second Paragraph, Rejection**

The Examiner rejected claims 1-22 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

Applicants regard as the invention. Specifically, the Examiner alleges that it is "unclear what the analyzing of the conservation property where the PCPs are conserved based on entropy and the final step of the PCPs based on eigenvectors have to do with one another and what the final step has to do with analysis of sequence data." The Examiner further alleges that the "outcome of the method is unclear."

The amended claim should make it clear that the step of "defining one or more PCP motifs in the multiple sequence alignment based at least on the detection of consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved according to at least one eigenvector" provides an output that may then be used "to search a sequence database resulting in identification of one or more related sequence segments having PCP characteristics similar to one or more of the PCP motifs," as currently recited in claim 1. In other words, to specifically answer the Examiner's question concerning "what the final step has to do with analysis of sequence data," the PCP motifs are used to search a sequence database to identify one or more related sequence segments.

Further, the information obtained by "analyzing the conservation property data for each of the PCP described sequence alignments to detect consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved based on at least the relative entropy determined for each column" (e.g., detected consecutive horizontal positions of the multiple sequence alignment) identify the portions of the multiple sequence alignment to be defined as PCP motifs. The PCP motifs are defined according to at least one eigenvector (e.g., such defined PCP motifs may matrices of numbers that represent the average value of each of 5 eigenvectors from the multidimensional scaling analysis of the amino acid properties at each position in the motif). In other words, the PCP motifs are defined according to at least one eigenvector, but in many circumstances, according to more than one eigenvector (e.g., 5 eigenvectors).

If for some reason such functional language is still unclear to the Examiner, the Examiner is requested to contact Applicants' attorney identified herein to further discuss this matter for clarification.

### **The 35 U.S.C. §103 Rejection**

The Examiner rejected claims 1-22 under 35 U.S.C. §103(a) as being unpatentable over Venkatarajan et al. (*J. Mol. Model*, 2001; 7:445-453) (hereinafter "the Venkatarajan reference") in further view of Zhu et al. (*Bioinformatics*, 2000;16:950-951) (hereinafter "the Zhu reference"), as evidenced by Mathura et al. (7<sup>th</sup> *Structural Biology Symposium*, 2002 May:93) (hereinafter "the Mathura reference"). Applicants respectfully traverse the rejection.

First, Applicants respectfully traverse such rejections in view of the fact that the Mathura reference used by the Examiner in the rejection of the pending claims is not an appropriate prior art reference under 35 U.S.C. §103(a) to be applied to the pending application, as pending U.S. Patent Application No. 10/817,530 claims priority to U.S. Provisional Application No. 60/460,769 filed 4 April 2003, the U.S. Provisional Application No. 60/460,769 included the information contained in the Mathura reference, and the Mathura reference was provided at the Structural Biology Symposium held May 17-19, 2002 which is less than one year prior to the filing of U.S. Provisional Application No. 60/460,769.

Further, it is believed that the Examiner cited the Mathura reference in rejection of the pending claims under 35 U.S.C. §103(a) because the Mathura reference is coauthored by the joint inventors of the above-identified pending application and another individual. Applicant submits a Declaration under 37 C.F.R. §1.132 declaring that Werner Braun, Catherine H. Schein, and Venkatarajan Mathura are the joint inventors of the claimed subject matter of the above-identified U.S. Patent Application No. 10/817,530 that is commonly disclosed in the Mathura reference and that the other co-author, Numan Oezguen, listed as an author on the Mathura reference did not directly participate in the subject matter claimed, or otherwise contribute to the claimed invention.

In view of the above and the attached Declaration, Werner Braun, Catherine H. Schein, and Venkatarajan Mathura are the joint inventors of the claimed subject matter that is commonly disclosed in the Mathura reference cited by the Examiner. As such, the Mathura reference cannot be used against the Applicant since the Mathura reference was presented at the Structural Biology Symposium on May 17-20, 2002 which is less than one year prior to the filing of U.S. Provisional Application No. 60/460,769 (of which the pending application claims benefit).

For this reason alone, it is respectfully requested that the rejection be withdrawn and the pending claims be allowed to issue.

Although further comments on the other references cited by the Examiner are considered unnecessary, it is noted that to establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations. The Venkatarajan reference and the Zhu reference do not teach or suggest all the claim limitations.

For example, claim 1 describes a method for use in sequence data analysis that includes providing a multiple sequence alignment of a plurality of sequences (i.e., wherein the multiple sequence alignment comprises a column of aligned amino acids and/or gaps for each horizontal position of the multiple sequence alignment). A plurality of numerical physical-chemical property (PCP) descriptors for each amino acid based on a plurality of physical-chemical properties thereof are provided (i.e., wherein each of the plurality of numerical PCP descriptors corresponds to one of "N" eigenvectors used in defining the amino acids in terms of physical-chemical properties). Each amino acid in the multiple sequence alignment is described quantitatively in terms of the plurality of PCP descriptors as a series of "N" eigenvectors resulting in "N" PCP described sequence alignments, wherein each PCP described sequence alignment corresponds to and is defined with numerical PCP descriptors which correspond to one of the "N" eigenvectors (e.g., each PCP described sequence alignment comprises a plurality of columns corresponding to the columns of the multiple sequence alignment). The method further includes analyzing each of the PCP described sequence alignments, on a column by column basis, to generate conservation property data for each column, wherein the conservation

property data for each column comprises an average value for the numerical PCP descriptors in the column and a standard deviation associated with the average value, and a relative entropy value for the column. The conservation property data for each of the PCP described sequence alignments is then analyzed to detect consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved based on at least the relative entropy determined for each column. One or more PCP motifs in the multiple sequence alignment are defined based at least on the detection of consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved. Such PCP motifs may be used to search a sequence database resulting in identification of one or more related sequence segments having PCP characteristics similar to one or more of the PCP motifs.

The Venkatarajan reference only describes the derivation of the eigenvectors and the methodology for defining the physicochemical properties of each amino acid in terms of 5 numbers, which represent over 200 different properties. Contrary to the Examiner's allegations, for example, there is no teaching or suggestion in the Venkatarajan reference that each amino acid in a multiple sequence alignment be described quantitatively in terms of the plurality of PCP descriptors as a series of "N" eigenvectors resulting in "N" PCP described sequence alignments. Further, for example, there is no teaching or suggestion in the Venkatarajan reference that each of the PCP described sequence alignments are analyzed, on a column by column basis, to generate conservation property data for each column, wherein the conservation property data for each column comprises an average value for the numerical PCP descriptors in the column and a standard deviation associated with the average value, and a relative entropy value for the column. Further, for example, there is no teaching or suggestion in the Venkatarajan reference that the conservation property data for each of the PCP described sequence alignments is then analyzed to detect consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved based on at least the relative entropy determined for each column. And yet further, for example, there is no teaching or suggestion in the Venkatarajan reference that one or more PCP motifs in the multiple

sequence alignment are defined based at least on the detection of consecutive horizontal positions of the multiple sequence alignment where the physical-chemical properties are conserved.

The Zhu reference does nothing to correct the deficiencies of the Venkatarajan reference. The Zhu reference describes the MASIA program for pattern recognition in multiple aligned protein sequences. The MASIA program is a distinct entity and very primitive in its approach to sequence searching. The MASIA program identifies areas in aligned protein sequences that match a user defined motif. The motif is directly encoded by the user, who can write a macro that defines the search criteria or use one of a series of prewritten macros at the site. The methodology of MASIA consists of being able to scan alignments in both horizontal and vertical directions.

The Zhu reference, however, contrary to the Examiner's allegations, does not cure the deficiencies in the Venkatarajan reference. For example, there is no teaching or suggestion in the Zhu reference to define PCP motifs as set forth in claim 1 to be, for example, used for searching one or more sequence databases. Rather, the motifs used in the Zhu reference are directly encoded by the user. Such user defined motifs are then used to search sequence databases.

The same or similar comments apply to claim 12, as well as the dependent claims which include the limitations of claims 1 or claim 12.

In view of the above information, for example, it is respectfully requested that the rejection under 35 U.S.C. §103(a) be withdrawn.



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**Summary**

It is respectfully submitted that the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted

By

Muetting, Raasch & Gebhardt, P.A.

P.O. Box 581415

Minneapolis, MN 55458-1415

Phone: (612) 305-1220

Facsimile: (612) 305-1228

**Customer Number 26813**

7 June 2007

Date

By: 

Mark J. Gebhardt

Reg. No. 35,518

Direct Dial (612) 305-1216

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The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to **Mail Stop Amendment**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Dani Monz

Name: Dani Monz

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